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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,423	03/20/2001	Richard Henry Jones	Q62257	7786

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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No. 09/719,423	Applicant(s) JONES ET AL.	
	Examiner Maury A. Audet	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, and 10-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary Amendment

1. Applicant's Preliminary Amendment, filed March 20, 2001, Paper No. 7, is acknowledged.

Requirement for Restriction Withdrawn

2. The present case was filed under 35 U.S.C. § 371, and is subject to the international rules of lack of unity, regarding restriction. The Examiner originally felt that the special technical feature linking the respective inventions (insulin compounds, compositions, and methods of use), namely 3,3',5' triiodothyronine (rT3), was sufficiently taught by reference HIRSHOWITZ et al. (Patent No. 6, 681, 561, Issued October 28, 1997), wherein specification column 3, lines 23-25 teaches a composition consisting of insulin and triiodothyronine (T3). Originally, restriction was required under 35 U.S.C. 121 and 372. The application was deemed to contain the following inventions or groups of inventions which were not so linked as to form a single general inventive concept under PCT Rule 13.1. In accordance with 37 CFR 1.499, applicant was required to elect a single invention to which the claims were restricted.

I. Claims 1-7, and 10-11, drawn to insulin compounds and compositions, classified in class 530, subclass 303.*

II. Claims 12-15, drawn to methods of use, classified in class 514, subclass 3.

During a telephone conversation with John Callahan, Attorney for Applicant, on March 3, 2003, a provisional election was made WITH traverse to prosecute the invention of Group I, claims 1-7, and 10-11. Claims 12-15 were withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Upon reconsideration, it has been determined that Hirshowitz et al., although teaching T3 with insulin, does not specifically teach the isomer rT3. Therefore, the requirement for restriction is withdrawn.

Status of the Claims

3. Claims 1-9 were originally filed in the present application. Claims 8-9 were cancelled, and new claims10-15 added by Preliminary Amendment, Paper No. 7. Claims 1-7, and 10-15 are pending in the present application and examined on the merits.

Domestic Priority under 35 U.S.C. § 120

4. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The specific applications noted in the declaration, which may want to be identified include: PCT/GB98/01722, filed June 12, 1998.

Information Disclosure Statement

5. The Information Disclosure Statement filed January 10, 2002 has been considered. An initialed copy of Form PTO-1449 in accordance with MPEP § 609 is attached.

Objections

6. On specification page 6, lines 19, 21, 32, and 35; and page 7, lines 2 and 5, reciting "125-Insulin". Assuming these refer to the same insulin corrected by preliminary amendment on page 4, lines 1 and 3, the above recited references lack consistency.

7. In claim 11, the first reference to "pharmaceutical" is misspelled.

8. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Amendment of the above objections is required.

Rejections

35 U.S.C. § 112, 1st ¶ Enablement

9. Claims 1-7, and 10-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for covalent binding of rT3 to human insulin residues B29 Lys and B1 Phe, does not reasonably provide enablement for covalent binding of rT3 to any insulin molecule at any residue (cl. 1), or to any lysine at any residue of any insulin (cl. 2), or to any amino acid of B1 residue of any insulin (cl. 3). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the

> courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for covalent binding of rT3 to any insulin molecule at any residue, or to any lysine residue of insulin or any amino acid at the B1 residue, for the following reasons:

The nature of the invention: The claimed invention is generally drawn to a compound or composition consisting of any insulin (at any residue) covalently bound to 3, 3', 5' triiodothyronine (rT3), and more specifically at a lysine residue or any amino acid at the B1 residue, which may be used in a method of treatment of the human or animal suffering from diabetes.

The state of the prior art and the predictability or lack thereof in the art: The human insulin molecule consists of 51 total amino acid residues, 21 in the A chain and 30 in the B chain. As with any protein molecule that interacts with a receptor, such as insulin, it is known that certain residues must be present for receptor activation, in order to stimulate systemic glucose uptake and utilization in skeletal muscle and adipose tissue and to suppress hepatic glucose production. It was not found in the art which residues are essential for insulin-insulin receptor activation. However, the art does teach that certain residues may be absent, without negatively impacting the insulin-insulin receptor activation. Havelund et al. (5,750,497, Issues

May 12, 1998) teach that "human insulin . . . Phe B1" may be deleted (claim 1(b)), as does Ertl et al. (6,221,633 B, Issued April 24, 2001; claim 1 and abstract). Ertl et al. also teach that residue B30 of a human insulin derivative may be absent. Although both Havelund et al. and Ertl et al. taught that many of the human insulin residues could be substituted with other amino acids, these references and the prior art referred to in each, did not teach that any other residues could be absent, beyond residues B1 and B30. Jones et al. teach covalent binding of T4 to a lysine at the B1 residue. A teaching was not found in the art as to whether B1 and B30 were 'inactive' in any insulin, beyond only human insulin. Therefore, the art appears to teach that rT3 could be bound to human insulin residues B1 or B30, or a lysine at human insulin residues B1 or B30, but it is unpredictable as to whether binding of rT3 to any other residue of any insulin would allow unaltered insulin-insulin receptor activation.

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification only teaches covalent binding of rT3 to residues B1 (Phe) and B29 (Lys) (or that the "B29 residue may be deleted"). Specification page 2 describes that the "rT3 moiety should be conjugated to a residue of the insulin molecule such that insulin activity is not adversely affected." Although this point is not elaborated on, nevertheless, the specification *does* acknowledge that specific residues (and assumably amino acids at those residues), must be present for unaffected insulin-insulin receptor activation. Guidance as to rT3 conjugation is only provided in two working examples: "through [either] the B1 residue of insulin . . . [or] [a]lternatively the B29 residue."

The breadth of the claims and the quantity of experimentation needed: The claims are drawn broadly to covalently binding of rT3 to any insulin at any residue, and the broad limitations of conjugation of rT3 to any lysine at any insulin residue and/or the B1 residue of any insulin. Absent sufficient teachings in the specification or art sufficient to overcome the teachings of unpredictability in the art as to enablement on whether rT3 can be covalently bound to any insulin at any residue, or to any lysine at any insulin residue and/or any B1 residue of any insulin, thus, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

35 U.S.C. § 103 Obviousness

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-7, and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Havelund et al. (5,750,497, Issued May 12, 1998, and recited by Applicant as WO-A-95/07931), in view of Weeks et al. (1997), and Ikeda et al. (1985).

The claimed invention is drawn to a compound consisting of any insulin molecule (at any residue (cl. 1), human insulin (cl. 4)) covalently bound to 3, 3', 5' triiodothyronine (any lysine residue (cl. 2), any amino acid at B1 residue (cl. 3)), used in a method of treatment of the human or animal body (cl. 5). The invention is further defined as a composition comprising a carrier and the compound of claim 1 (cl. 6), or claim 3 (cl. 10), and a pharmaceutical composition comprising an excipient and the compound of claim 1 (cl. 7), or claim 3 (cl. 11). The invention

is additionally defined as a method of treatment of a human or other animal, suffering from diabetes (cl. 14), by insulin replacement therapy (cl. 12), through administration (cl. 13) into the circulation (cl. 15).

Havelund et al. teach the compound human insulin acylated (covalent bond created) to tetraiiodothyroacetic acid (thyroxine) at the lysine residue (B29) (Example 20 at column 28), in the treatment of the human or animal body (diabetes) (claim 95; column 1, line 13), wherein the B1 residue may be deleted (claim 1). Havelund et al. further teaches composition/ pharmaceutical composition in an aqueous solution (carrier) comprising an insulin derivative and an isotonic agent (excipient) (cl. 78). Havelund et al. does not specifically teach a compound/composition consisting of thyroxine (T4) derivative 3, 3', 5' triiodothyranine (rT3) covalently bound to the B1 residue of insulin.

Weeks et al. teach:

> The overall function of T4 and T3 are similar though much of the biological activity may be the result of monodeiodination to 3,5,3'-triiodothyronine prior to interacting with target cells. Under certain conditions (protein starvation, malnutrition, stress, obesity (high carbohydrate) certain diseases of excretory and metabolic organs (liver and kidney), febrile illness, etc.) thyroxine is preferentially monodeiodinated to 3,3',5'-triiodothryonine ("reverse T3"). Since this form of T3 formed by target cells is biologically inactive, monodeiodination to form "reverse T3" provides a mechanism to attenuate the metabolic effects of thyroid hormones" (page 2).

Ikeda et al., teach that "is well known that T4 is largely metabolized to T3 and rT3 by deiodination in . . . the liver" (page 647, 1st ¶). As described by Weeks et al. and Ikeda et al., rT3, like T4, is a thyroid hormone deiodinated by one iodine molecule from T4, and having the benefit of hepatoselectivity without thyroid stimulation. One of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to substitute T4 with another known thyroid hormone such as rT3, in a compound or composition directed towards

diabetic therapy, because it was known that rT3 retains hepatoselectivity (Ikeda et al.), and had the added benefit of not stimulating thyroid activity (Weeks et al.).

35 U.S.C. § 101: Double Patenting – Non-Statutory

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, and 10-15, summarized supra, are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, and 5-12 of Jones et al. (5,854,208) in view of Ikeda et al. (1995), and Havelund et al. (5,750,497).

Jones et al., teaches "a hepatoselective insulin which is formed of insulin or a functional equivalent of insulin covalently bound to a molecule having an affinity for one or more binding proteins naturally present in the circulation of a human or an animal . . . wherein the molecule is a naturally occurring hormone or an analogue of a naturally occurring hormone . . . a thyroid hormone" (cl.'s 1-3), wherein "the molecule is bound to the B1 lysine" (cl. 5-6). Jones et al. further teaches the above limitations in a pharmaceutical composition including an excipient (cl. 7-12). Although Jones et al.'s broad claims 1-3 teach rT3 bound to insulin as an equivalent of T4 bound to insulin, the specification does not specifically describe this compound. Jones et al.

does claim the binding of the molecule to a lysine (B1), but not specifically the B29 lysine (see 35 U.S.C. § 112, 1st ¶ rejections supra). Also, Jones et al. does not claim a method of use, but teaches the use of the compound/composition as a method of treatment of diabetes mellitus (column 1), and demonstrates its use on an animal (column 9).

Ikeda et al. teach that it "is well known that T4 is largely metabolized to T3 and rT3 by deiodination in . . . the liver" (page 647, 1st ¶). As described, rT3 is a molecule that has affinity for binding proteins within the liver of humans and animals, is a naturally occurring hormone (like T4 and T3), and is specifically a thyroid hormone. One of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to covalently bind rT3 to insulin, like T4, since rT3 is a naturally occurring thyroid hormone.

Havelund et al. teach the compound human insulin acylated (covalent bond created) to tetraiiodothyroacetic acid (thyroxine or T4) at the lysine residue (B29) (Example 20 at column 28). As discussed supra, T4, like rT3 is a naturally occurring thyroid hormone. One of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to covalently bind the rT3 to a lysine (Jones et al.) at the B29 residue, in view of Havelund et al.

Havelund et al., teach the use of the T4/B29 insulin compound in a method of treating a patient (animal/human) suffering from diabetes (claim 95). Jones et al. described the use of the T4/B1 insulin in a method of treating diabetes. One of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to use rT3 bound to the lysine residue at B1 residue (or B29 residue), since rT3 like T4 naturally occurring thyroid hormone, and in view of Havelund et al.'s specific claiming of such a method.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
March 13, 2003

Brenda Brumback

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